The association between idiopathic thrombocytopenic purpura and cardiovascular disease

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The Association between Idiopathic Thrombocytopenic Purpura and Cardiovascular Disease: A retrospective cohort study

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Essentials:

- We estimated the cardiovascular risk of patients with Idiopathic Thrombocytopenic Purpura (ITP)
- The risk of cardiovascular disease was 38% higher in ITP patients compared to controls
- Among the ITP patients, splenectomy was associated with higher cardiovascular disease
- Clinicians should consider cardiovascular risk when managing ITP patients

Abstract:

Background: Idiopathic Thrombocytopenic Purpura (ITP) is classically characterized by a transient or persistent decrease of platelet count. Mortality is higher in the ITP population than the general population, with a possible association to increased cardiovascular disease (CVD).

Objectives: The objective was to assess the strength of the association between ITP and CVD, with a secondary aim to assess the impact of splenectomy on CVD.

Methods: A population-based retrospective, open cohort study using clinical codes was performed using data from 6,591 patients with ITP and 24,275 randomly matched controls (up to 1:4 ratio matched by age, sex, body mass index and smoking status). The main outcome was the risk of CVD which included ischemic heart disease, stroke, trans-ischemic attack and heart failure. Adjusted incidence rate ratios were calculated using Poisson regression.

Results: During a median 6-year observation period there was a CVD diagnosis recorded in 392 (5·9%) of ITP patients and 1,114 (4·5%) of control patients. There was an increased risk of developing CVD in the ITP cohort (adjusted IRR 1·38; CI 95% 1·23-1.55), which remained robust even after a sensitivity analysis only including incident cases of ITP. Findings suggested that patients who have undergone splenectomy were at even further increased risk of developing CVD when

comparing to the ITP population who had not undergone splenectomy (adjusted IRR 1·69; CI 95% 1·22-2·34).

Conclusion: There is an increased risk of developing CVD in patients with ITP and even further increased risk for those patients with ITP who underwent splenectomy.

Keywords:

Purpura, Thrombocytopenic, Idiopathic

Blood platelet disorders

Thrombocytopenia

Retrospective Studies

Cardiovascular Diseases

Introduction:

Idiopathic Thrombocytopenic Purpura (ITP) is an acquired immune-mediated disease defined as a transient or persistent decrease of platelet count.[1,2] The decreased platelet count in ITP is associated with an increased rate of bleeding, hemorrhage related outcomes[3] and abnormal platelet activity.[4] Global incidence rate for ITP in adults are

estimated to be 1·6-3·9/100,000 persons with prevalence rates estimated at 5·6-20/100,000 population.[5] Prevalence reported in UK is particularly high with an estimated incidence of 3·9/100,000 persons and a prevalence of 50/100,000 population.[6,7]

It has been well established that mortality is higher within the ITP cohort than the general population.[8,9] Previous population based studies have also identified a comparatively higher incidence of diabetes, acute/chronic renal failure, leukemia, and Hodgkin's disease within the ITP cohort.[8] An increased incidence in any vascular event (IRR 1·0 95% CI 1·41-2·05) and particularly unstable angina, ischemic stroke and TIA have been identified in a cohort study conducted in the United States utilizing insurance data.[8] However there has been conflicting evidence surrounding the nature and strength of the association between myocardial infarction (MI) and ITP.[8,10] The only study conducted in UK looked at multiple conditions and did not account for the time to event or adjust for important confounders.[10]

The pathophysiology by which ITP affects cardiovascular disease is unclear. Platelet destruction releases humoral factors and platelet micro-particles (PMPs)[11] which are elevated in ITP patients.[12] PMPs induce thrombin and coagulation

activations, which may increase thrombotic outcomes.[13] ITP patients often have elevated pro-inflammatory cytokines suggesting an inflammatory etiology.[14,15] Inflammatory activity may also affect coagulation states which could put individuals at risk of thrombotic events.[16]

The mainstay of treatment for ITP (based on severity deemed by platelet count) is the use of glucocorticosteroids. The majority of ITP cases are steroid-responsive and total remission can be achieved in 33% of cases.[17] Partial or total splenectomy is an alternative treatment for adult patients not responding to glucocorticoid therapy with remission of ITP in two-thirds of cases.[18] Splenectomy is not without risk, and even the laparoscopic approach bears significant risk of surgical complications (9.6%).[18] It has been identified that ITP patients who undergo splenectomy are at a higher risk of venous thromboembolic events.[19] The pathophysiological link is unclear. There is evidence to suggest that splenectomy may lead to both thrombocytosis and an increased number of damaged red cells. This induces a hypercoagulable state with increase thrombotic risk.[20–22] Post-splenectomy patients have been shown to have even higher levels of cellular micro-particles (C-MPs) which further promotes hypercoagulability.[23]

This study aims to explore the association between ITP and cardio-vascular disease as well as attempt to identify the impact of splenectomy on this association.

Methods:

Study Design:

A population based, retrospective open cohort study in which patients diagnosed with ITP were compared to healthy controls matched by age, sex, body mass index (BMI) and smoking status. The Health Improvement Network (THIN) has been demonstrated to be broadly representative of the U.K. population.[24]

Data Source:

The THIN database comprises of UK electronically recorded medical records in primary care, with the purpose of the database to encourage research in order to improve health care delivery. The THIN database comprises of 675 UK general practices, compiling data of over 14 million patients, of which over approximately 3.6 million who are actively registered broadly representative of the UK population.[25] Patient information is entered into Vision patient record software

which uses Read code data (Clinical code)[26], rather than the International Classification of Diseases (ICD) codes. The Vision software also captures laboratory results as well as some British National Formulary Drug prescription records.[27] The University of Birmingham holds a data sharing agreement with IMSHealth (the providers of THIN) to allow for data to be used for research under the Data Protection Act (1998). [28]

Study Population:

The study population consisted of patients diagnosed with ITP (exposed) and controls not diagnosed with ITP (unexposed) during the study period from 1st of January 1996 to the 1st of September 2015.

Individual practices were eligible for inclusion in the study from the later of the following two dates to ensure that the practice was making full use of their system and not under-recording important outcomes: one year after the date their practice system was installed; and the practice's acceptable mortality recording (AMR) date. Individual patients will be eligible for inclusion from the latest of the following dates to ensure that there was sufficient time for baseline data on comorbidities to have been recorded; the date their practice

became eligible for inclusion; and a year after registration with their practice to allow for the recording of comorbidities.

Selection Criteria:

Follow-up start date for an indexed patient (index date) in the exposed group was set at first documentation of ITP once a patient was eligible to take part in the study (newly diagnosed patients/incident cases) or the date a patient became eligible to take part in the study, if they already have a diagnosis of ITP (patients with an existing diagnosis/prevalent cases) (Appendix 1). The same index date was assigned for their matched corresponding unexposed patients to mitigate immortality time bias. Both the exposed group (ITP) and unexposed group (control) were followed up from the index date until the first of the following events (exit date): patient died; patient left practice; last data collection from practice; study end date; patient diagnosed with cardiovascular disease (stroke or ischemic heart disease, myocardial infarction and angina).

Patients were excluded from the study if they had a diagnosis of CVD prior to the index date of the study. Individuals were included in the exposed group if they had a recorded diagnosis

of ITP (Appendix 2) using clinical codes (https://digital.nhs.uk/article/1104/Read-Codes). ITP codes were validated from previous studies where read codes were used to identify exposed ITP patients.[29,30] In the U.K, the diagnosis of ITP is made by a hematologist in a secondary/tertiary setting which is then relayed to the GP, whose responsibility it would be to record this on the patient's electronic medical record. The diagnostic criteria for identifying ITP in the UK secondary care setting is based on the "British Committee for Standards in Hematology" guideline. [31] A record of splenectomy also identified through clinical codes (Appendix 2) was also recorded at this point. Each ITP patient was then matched to 4 control patients in the unexposed cohort and were randomly selected from the same General Practice. Controls were individually matched to cases on age at index date (to within 2 years), BMI (to within 2 Kg/m2), smoking status and gender.

Outcomes:

The primary outcome was the development of a large vessel atherosclerotic/thrombotic cardiovascular event (Ischemic heart disease, heart failure and Stroke/TIA during the observation period as well as a composite outcome of all three) identified through clinical codes (Appendix 4). Recording of CVD is

accurate in UK primary care because there is a mandatory requirement for maintaining a register for cardiovascular disease and incentive payments are made for identification and management of CVD [32].

Co-Variates:

Well known co-variates which impact on the development of cardiovascular disease were identified in the study population baseline data. These included hypertension, diabetes mellitus, inherited thrombophilias, co-morbidity identified through the Charlson co-morbidity index, the use of lipid lowering medications, anti-platelet agent medications and warfarin medications that were identified through clinical codes inputted by GPs in primary care (Appendix 3).

Statistical analysis plan:

Baseline characteristics were descriptively compared between the groups. Comparison was assessed either using chi –squared (sex, Townsend deprivation score, smoking status, hypertension, diabetes mellitus, inherited thrombophilias, Charlson co-morbidity index, the use of lipid lowering medications, anti-platelet agent medications, warfarin medications), student t-test (age and BMI) or Mann-Whitney U test (person years).

An estimated incidence rate ratio was calculated for each outcome. Then adjusted incidence rate ratios were calculated using Poisson regression adjusting for individual patient covariates (age, sex, Townsend deprivation score, smoking status, hypertension, diabetes mellitus, inherited thrombophilias, Charlson co-morbidity index, the use of lipid lowering medications, anti-platelet agent medications, warfarin medications to account for any variation in consultation practice). BMI was treated as a categorical variable to address missing values. Incidence rate ratios were calculated with 95% confidence and a statistical significance threshold of $p<0{\cdot}05$.

As a secondary analysis, we also assessed the impact of splenectomy on patient outcomes. We looked at the risk of cardiovascular disease within the ITP patients stratified by those who had splenectomy and those who did not. This allowed for analysis of the isolated impact of splenectomy in the exposed group.

In a sensitivity analysis, we restricted the investigation of occurrence of cardiovascular disease to only patients with incident diagnoses of ITP and their respective matched controls during the study period to account for survival bias that may underestimate or overestimate the effect size.

All analysis was conducted using Stata v14.0 software. The THIN data collection scheme received multi-center research ethics committee (MREC) approval in 2003 with scientific committee approval of this particular study in March 2017 (SRC 17THIN024) from 'IMSHealth' (data provider).

Role of the funding source:

There is no funding source to declare in this study.

Results:

Baseline Characteristics:

A total of 6,591 patients with ITP were identified on the THIN database and matched to 24,275 controls (on 1:4 ratio). The mean length of follow up in the ITP and control population, was 5.6 years (SD 4.5 years) and 6 years (SD 4·6 years) respectively.

Mean patient age within the ITP cohort was 48.4 years (SD 19·1 years) with significantly more females than males (58·6% vs. 41·3% respectively). In general, there was a significant difference in the proportion of patients with diabetes and lipid lowering medications between the ITP and control cohort.

Baseline characteristics are described in further detail in Table 1 (Missing values are in appendix 7). In the ITP group, there were 506 (7·6%) patients with splenectomy at study entry and an additional 162 splenectomies (in total 668;10·1%) during follow-up period. Three hundred and fifty-three (5·4%) patients were on active treatment with steroids at baseline.

Association between cardiovascular disease and ITP:

During the observation period 392 (5·9%) and 1,114 (4·5%) patients in the ITP and control groups respectively experienced cardiovascular event. The incidence rate was 11 and 8 per 1000 person years respectively. The adjusted incidence rate ratio of all cardiovascular disease was found to be significantly higher in the ITP cohort compared to the control cohort (adjusted IRR 1·38; CI 95% 1·23-1.55, P<0.001). Further sub-analysis was carried out to compare the incidence of Ischemic heart disease, stroke/TIA, and heart failure separately in these cohorts. Following sub-analysis, the ITP cohort demonstrated increased adjusted incidence rate ratios of Ischemic heart disease (IRR 1·21; CI 95% 1·01-1·44, P=0.034), Stroke or TIA (IRR 1·39; CI 95% 1·17-1·66, P<0.001) and heart failure or left

ventricular dysfunction (IRR 1·42; CI 95% 1·12-1·81, P=0.004). (*Table 2).*

The impact of splenectomy on cardiovascular disease in the ITP cohort:

ITP patients with splenectomy at baseline had an increased adjusted (Adjusted for age, sex, Townsend deprivation score, smoking status, hypertension, diabetes mellitus and the use of lipid lowering medications, steroid use, Charlson co-morbidity index, anti-platelets, inherited thrombophilias, and warfarin use) incidence rate ratio of cardiovascular disease compared to ITP patients who did not have splenectomy (adjusted IRR 1·69; CI 95% 1·22-2·34, P=0·001). Active steroid treatment at baseline also had an increased incidence rate ratio for cardiovascular disease compared to ITP patients who did not have steroid treatment (adjusted IRR 1·49; CI 95% 1·07-2·08, P=0·017).

Additional Analysis

Results of an analysis also adjusting for consultation rate showed similar results (appendix 5), with an adjusted incidence rate ratio for cardiovascular disease significantly greater in ITP patient (1·49; CI 95% 1·33-1·67). An analysis restricted to incident ITP patients also showed concurrent results (appendix 6). The adjusted incidence rate ratio for cardiovascular disease

was significantly greater in ITP patients compared to controls in incident only cases (1·38; CI 95% 1·15-1·66).

Discussion:

Summary of Key Results:

This study found that individuals with ITP were at a higher risk of developing all types of CVD (adjusted IRR 1·38; CI 95% 1·23-1.55, P<0.001). when compared to individuals without ITP over the observation period. These findings remained once adjusted for clinically significant risk factors for developing CVD. We also demonstrated that patients who have undergone splenectomy were at even further increased risk of developing CVD when comparing to the ITP population at baseline who had not undergone splenectomy (adjusted IRR 1·69; CI 95% 1·22-2·34, P=0·001).

Compared to Current Literature:

The results of this study builds on the current literature surrounding ITP and CVD risk. ITP is an autoimmune condition characterized by a low platelet count and bleeding, but conversely individuals with ITP may show an increased

thrombotic and atherosclerotic risk[33] hypothesized to be due to PMP cascade. An American epidemiological study has demonstrated some of the significant associations between; ITP and TIA (IRR 1·69; CI 95% 1·21-2·35), ITP and stroke (IRR 2·05; CI 95% 1·26-3·36) and insignificant association between ITP and MI (IRR 0.80; CI 95% 0.49-1.30).[8] Whereas General Practice Research Database (GPRD) data from the U.K. has previously shown a significantly positive association between ITP and; MI (OR 4·71; CI 95% 2·21-10·06), left ventricular failure (OR 2·94; CI 95% 1·43-6·06) and cerebrovascular accident (OR 2·30; CI 95% 1·21-4·38).[10] The results of this study are confirmatory of the findings of the previous studies and addressed the methodological limitations noted in them.

Though the link between splenectomy and venous thromboembolic events has been explored [20–22] and hypothesized to be due to a hyper-coagulable state, the link between splenectomy and arterial events had not been fully explored. Therefore, the authors believe this is the first study to identify that individuals who have undergone a splenectomy appear to be at an adjusted significantly increased risk of developing CVD (adjusted IRR 1·69; CI 95% 1·22-2·34, P=0·001), even greater than the risk for those who have not undergone a splenectomy procedure.

Study Limitations:

The findings of this study should be interpreted in context of its limitations, some of which are inherent to this design of study. The THIN database is populated using clinical codes classified by General Practitioners (GPs) following consultations with individuals. Therefore, the validity of the coding will be affected by the coding practices of individuals with some patients being misclassified. Every effort was taken to overcome this by selecting a list of multiple clinical codes for ITP and splenectomy to ensure every coding combination was taken into consideration. We did not account for the severity of the disease which may have given further insight. This may have affected the splenectomy sub-group analysis as individuals who have undergone splenectomy will generally have a more severe form of ITP which in turn could have increased their risk of developing CVD outcomes. The aims of this study were to identify associations rather than causality due to the nature of data being analyzed. However, this study has not only been able to demonstrate some important associations regarding ITP and CVD, it has shown that patients who have had splenectomy as a consequence of ITP may be at increased risk of CVD. On the other hand, when communicating risks to

patients or the public, caution is advised given the absolute risk difference in this young studied population (Median age 48·5 years) with a median follow up of 5·6 years, was notably low (3 per 1,000 person years).

Conclusion:

Our study shows there is an association between ITP and an increased risk of developing CVD. Secondly the study shows a strong association with the increased risk of developing CVD in ITP patients who underwent a splenectomy. Physicians should routinely evaluate for cardiovascular symptoms and manage risk factors for cardiovascular disease optimally in patients with ITP. Decision on offering splenectomy to patients with ITP should take into consideration future increased risk of cardiovascular disease. Further research utilizing ITP registries and cohorts in other countries are needed confirm the risk observed in our study. Mechanisms that promote cardiovascular disease in ITP patients should be further studied in a laboratory setting.

Declaration of Interests:

There are no conflicts of interest to be declared by the authors of the work.

Authors contributions:

JSC and TT were responsible for initial drafts in protocol design, data extraction, initial analysis and final write up. SL assisted in writing up the paper and as a specialty hematologist was able to provide expert opinion on the paper. TM and BW assisted during the write up stage and made significant amendments during this stage. KN and PG provided contributions by overlooking the paper as the lead supervisors with KN being the corresponding author. KN assisted during the protocol stage, data extraction, analysis and write up. PG assisted during protocol and write up stages.

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